



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>3</sup> :  A61K 39/00, 45/02	A1	(11) International Publication Number: WO 85/ 00974 (43) International Publication Date: 14 March 1985 (14.03.85)
(21) International Application Number: PCT/US84/01389 (22) International Filing Date: 31 August 1984 (31.08.84) (31) Priority Application Number: 8323428 (32) Priority Date: 1 September 1983 (01.09.83) (33) Priority Country: GB (71) Applicant (for all designated States except US): HYBRI-TECH INCORPORATED [US/US]; 11085 Torreyana Road, San Diego, CA 92121 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : FRINCKE, James, M. [US/US]; 339 Shoemaker Lane, Solana Beach, CA 92075 (US). UNGER, Barbara, W. [US/US]; 13890 Amber Sky Lane, San Diego, CA 92121 (US). BURNETT, Karen, G. [US/US]; 3814 Martha Street, San Diego, CA 92117 (US). HERSH, Evan, Manuel [US/US]; 9 Falling Leaf, Houston, TX 77024 (US). ROSENBLUM, Michael, Gordon [US/US]; 8802 Ilona Lane, No. 2, Houston, TX 77025 (US). GUTTERMAN, Jordan, Udell [US/US]; 5943 Yarwell Drive, Houston, TX 77035 (US).	(74) Agents: BERMAN, Charles et al.; Lyon & Lyon, 611 West Sixth Street, 34th Floor, Los Angeles, CA 90017 (US). (81) Designated States: AU, DK, FI, JP, NO, US. Published With international search report.	
(54) Title: ANTIBODY COMPOSITIONS OF THERAPEUTIC AGENTS HAVING AN EXTENDED SERUM HALF-LIFE  (57) Abstract  A complex of alpha-interferon with a monoclonal antibody complexes with the alpha-interferon without impairing its antiviral activity. The serum half-life of the interferon administered as the complex is substantially increased when compared to that of alpha-interferon administered alone.		

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DESCRIPTIONANTIBODY COMPOSITIONS OF THERAPEUTIC  
AGENTS HAVING AN EXTENDED SERUM HALF-LIFEField of the Invention

This invention relates to therapeutically active agents and the treatment of disease therewith. In another aspect, it relates to antibody complexes of a therapeutically active agent. In a more specific aspect, it relates to complexes of a monoclonal antibody and a therapeutically active agent and their use in the treatment of disease.

Background

10 It is almost a trite observation to note that the use of a broad spectrum of drugs to treat human and other mammalian disease is routine medical and veterinary practice. Therapeutically active agents, however, often suffer from a number of shortcomings which limit and  
15 complicate their use. A particular problem is that, after administration to the patient, a drug may be so rapidly cleared from the body by metabolic or other pathways or otherwise biologically inactivated so that only a relatively small percentage of the drug administered actually has a therapeutic effect. To compensate  
20 for this problem, it is common practice to increase the dosage of the drug and/or to prolong its period of administration and/or to shorten the interval between doses so that the therapeutically effective concentration of the  
25 drug in the patient is maintained for a period sufficient to achieve the desired result.

These procedures are useful but have their own limitations. Increasing the dosage may be limited, for example, in the case of intramuscular administration, by  
30 the bolus which can be tolerated. Many drugs have toxic



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side effects which may limit the dosage duration or interval which can be safely used. In some cases, promising drugs cannot be used because side reactions are so severe that an effective therapeutic dose cannot be  
5 safely administered. The need to administer multiple small doses of a drug or to use continuous infusion techniques increases the cost of treatment and the burden on hospital personnel, and, of course, adds to the patient's discomfort.

10 Accordingly, there exists a need for means by which the therapeutically active concentration of a drug, after administration, is maintained for a longer time.

#### Summary of the Invention

It is the normal and expected function of antibodies  
15 to complex with foreign substances to more rapidly clear them from the body. We, however, have unexpectedly found that the serum or plasma half-life of a therapeutically active agent can be extended by forming a complex of the agent with a selected antibody, preferably a monoclonal  
20 antibody, which binds to the agent at a site which does not substantially impair its therapeutic activity and which extends the serum half-life of the agent. Thus, as used herein, the term "antibody" means a monoclonal antibody or polyclonal antibodies unless otherwise  
25 specified or required by the context. According to our invention, the complex of the therapeutically active agent and the antibody may be formed in vitro and then administered. Alternatively, the agent and antibody may be administered at the same time. In yet another alterna-  
30 tive, the antibody may be administered first, and after an interval during which its distribution in the patient approaches equilibrium, the therapeutically active agent can be administered.

By selecting the proper antibody for forming the  
35 antibody: drug complex, the serum half-life and, thus, the effective concentration of the therapeutically active



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agent, can be maintained in vivo for a longer interval. While monoclonal antibodies are preferred for use in the invention, it is also within the scope of the invention to use polyclonal antibodies against the therapeutically active agent which complex with the therapeutically active agent without materially impairing its therapeutic activity.

Accordingly, it is an object of the present invention to provide means by which the serum half-life of a therapeutically active agent is extended.

Another object of the invention is to provide compositions which increase the effective lifetime of a therapeutic agent in vivo after administration to a patient.

#### 15 Detailed Description of the Invention

As indicated above, the present invention, in one embodiment, is a complex between a therapeutically active agent with a monoclonal antibody selected to bind the therapeutic agent at a site which does not materially impair its therapeutic activity but which forms a complex with the agent to confer upon the agent a serum half-life longer than that of the therapeutic agent alone and approaching the serum half-life of the antibody. Alternatively, the invention comprises a similar complex of therapeutic agent with polyclonal antibodies selected to bind the antibody without materially impairing its therapeutic activity and which form a complex having an extended serum half-life.

In another embodiment, the invention is a process involving the administration to a host of a complex comprising the therapeutic agent and either a monoclonal antibody or polyclonal antibodies having the properties noted above. The process of the present invention also includes either simultaneous administration of the therapeutics agent and a suitable antibody preparation or an



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initial administration of the antibody preparation followed by administration of the therapeutic agent after the antibody has had an opportunity to distribute itself throughout the host.

5       The therapeutic agents useful in the invention are those which are or can be made immunogenic, i.e., those for which an immune response can be obtained either directly or, in the case of a hapten, by binding the agent to a molecule which is immunogenic. Monoclonal antibodies  
10 against the therapeutic agent can be obtained by methods which are now well known to the art and which need not be described in detail. These methods generally involve immunization of a mouse or other animal species, usually mammalian or avian, with the immunogen. Human lymphoid  
15 cells may also be obtained after immunization (natural or induced) or may be sensitized in vitro. After an immune response is generated, spleen cells of the immunized mouse or other immune lymphoid cells are fused with cells of an established lymphoid tumor line using known techniques to  
20 form hybridomas which produce monoclonal antibodies. Clones of hybridomas are screened to select those which are producing monoclonal antibodies that are specific for the antigen of choice, in this case the therapeutic agent. Monoclonal antibodies having the desired specificity  
25 are further screened to select those that form an antibody:agent complex in which the agent retains all, or substantially all, of its therapeutic activity. These complexes are further screened to select those which have an extended serum half-life. In certain circumstances,  
30 it can be beneficial to use a mixture of two or more monoclonal antibodies. In some circumstances it may also be desirable to use a stoichiometric excess of antibody.

Polyclonal antibodies useful in the invention are  
35 obtained by well known techniques as well. These include stimulating an immune response against the therapeutic agent, or fragment thereof, in a suitable animal host such



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as a rabbit or other mammal. Chickens and other avian species can also be used. Serum taken from the host is subjected to affinity purification to isolate polyclonal antibodies against the therapeutic agent. These  
5 antibodies are subsequently fractionated, if necessary, to isolate a subpopulation which complexes with the therapeutic agent without materially impairing its desirable activity.

Particularly preferred for use in the invention are  
10 human antibodies against the therapeutic agent produced by hybridomas which, for example, are the product of fusion of a human B-lymphocyte with an established mammalian lymphoid line, e.g., a human or mouse myeloma line.

As used herein, the term antibody includes fragments  
15 thereof such as Fab, Fab', and Fab'2 or mixtures thereof and including mixtures with whole antibody. Such fractions may be less immunogenic in some patients and may also better allow better penetration of the agent to the target site.

20 In certain applications, the monoclonal antibody is preferably a hybrid antibody having a dual specificity, one against the therapeutically active agent and the other against another antigen, for example, an antigen associated with the disease which it is desired to treat with  
25 the agent. Among these may be mentioned tumor associated antigens such as carcinoembryonic antigen (CEA), prostatic acid phosphatase (PAP), ferritin and prostate specific antigen (PSA). In such cases, the other specificity could be selected to bind with an agent which has anti-tumor  
30 activity. For example, the second specificity could be against a toxin such as ricin or an interferon. Processes for obtaining such hybrids are disclosed in the pending patent application of J. Martinis et al., Serial No. 367,784, filed April 12, 1983, assigned to Hybritech Inc.,  
35 an assignee of this application, the disclosure of which is incorporated by reference.



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Among the therapeutic agents which are useful in the invention may be mentioned drugs such as adriamycin, vincristine, genomycin mitomycin C, and prostacyline; toxins such as abrin and ricin; and biological proteins  
5 such as the interferons (alpha, beta and gamma), the interleukins, hormones such as insulin, plasminogen activators such as urokinase, streptokinase and tissue plasminogen activator, growth factors such as nerve growth factors, and platelet activating factor. Particularly  
10 useful are complexes of a monoclonal antibody and one of the interferons, for example, alpha-interferon. As used herein, the term "interferon" is used to include those agents having the characteristics attributed to interferons as described in Interferon: An Overview, Ion

15 Gresser, Ed., 4 (1982), p. 4, which is incorporated herein DNA technology which is identical to a naturally occurring interferon or which differs therefrom by one or more of the following:

1. a difference in amino acid sequence;
- 20 2. a difference in chain folding;
3. a difference in carbohydrate substitution.

The utility of the present invention is shown by the experiments described below with alpha-interferon. In that regard, alpha-interferon, a multi-species interferon,  
25 has been shown to have a therapeutic effect in the treatment of certain malignant tumors including breast cancer, multiple myeloma and malignant lymphoma. However, it has been shown to rapidly clear from the plasma of man and animals during clinical trials. This has been compensated  
30 for by giving a high dose intra-muscularly. However, the maximum dose is limited because of high-dose toxic side effects. Also, the high doses used are very expensive and may elicit an immune response in a substantial number of patients treated.



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Experimental Details1. Preparation of anti-                   -interferon monoclonal  
antibodies:

Balb/c mice were immunized with partially purified  
5 leukocyte interferon. Spleen cells from immunized mice  
were fused with a myeloma line (either the NS-1 or SP2/0  
lines) to produce hybridomas. The hybridomas were  
screened to select those reactive with <sup>125</sup>I-labeled  
interferon in a radioimmunoassay wherein the immune  
10 complexes were removed by horse anti-mouse IgG bound to  
sepharose beads. Interferon used in immunization and  
screening were from the same source. Antibodies were  
selected for positive reactivity with interferon. Hybri-  
domas producing the selected antibodies were cloned  
15 by limiting dilution to ensure homogeneity of the cell  
population.

2. Testing for Reactivity of an Antibody:Interferon  
Immune Complex in the Anti-Viral Protection Assay

Approximately 40 anti-alpha interferon monoclonal  
20 antibodies were employed to make interferon:antibody  
immune complexes which were tested for retention of  
anti-viral activity using the standard method described,  
for example, in Rubinstein, et al., J. Virology, 37,  
755 (1981). The first step in this procedure was forma-  
25 tion of the immune complex by the addition of ascitic  
fluid to the anti-viral protection assay mixture which was  
monitored for inhibition of interferon activity. Ten of  
the forty antibodies were selected for further investiga-  
tion because they did not inhibit the viral protection  
30 properties of the interferon in this assay. These anti-  
bodies were then further concentrated with sodium sulfate  
and re-tested. In each case, non-inhibition of anti-viral  
activity as verified. To demonstrate whether complexes of  
interferon with these antibodies were actually formed, the  
35 reaction mixtures were adsorbed with solid phase sepharose  
bound sheep anti-mouse IgG to remove the antibody and  
complexed interferon. The supernatant from the sepharose



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adsorptions were then tested in the standard antiviral protection assay. In the case of one particular antibody, designated IFG 252.2 by us, the antiviral protection was almost completely removed from the supernatant during the adsorption. Controls were performed to ensure this phenomena was not due to non-specific absorption during the sepharose adsorption step. These data demonstrate that this antibody binds efficiently and avidly to interferon without inhibiting its antiviral activity.

Another known biological property of alpha interferon is its inhibition of cellular proliferation. In an assay system using DAUDI cells, retention of anti-proliferative activity was demonstrated for alpha interferon in the presence of the IFG 252.2 antibody. These data demonstrate that IFG 252.2 also binds alpha-interferon without affecting its anti-proliferative activity.

### 3. Administration of Alpha-Interferon:IFG 252.2

#### Complex to Laboratory Rats

A Fisher rat (250-260 g) was lightly anesthetized with sodium thiopental. A plastic canula was then surgically inserted into the femoral artery of the other leg. A bolus dose of alpha-interferon (Clone A of Goeddel et al., Nature, 290, 20-26 (1981), 7600 units total in 0.5 ml phosphate buffered saline) was administered over 2 seconds into the venous catheter. Blood samples (0.5 ml) were withdrawn at various times from the arterial catheter. After each blood withdrawal, 0.5 ml of PBS were injected via the venous catheter. The samples were centrifuged, the plasma decanted and analyzed for interferon anti-viral activity by standard methods. In a second rat, the same amount of interferon was preincubated with IFG 252.2 (38 microgram/microliter = 190 micrograms antibody) and then administered through the venous catheter. Blood samples were taken and analyzed in the same way as for the first. The results of these experiments were then plotted and subjected to nonlinear regression analysis.



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These results indicate that the activity of alpha-interferon in the rat without added anti-interferon has a two phase disappearance curve. The alpha-phase has a 6.8 minute half-life with a two log reduction of interferon activity in the plasma at 30 minutes. The volume of distribution is 20.8 ml. At 30 minutes a beta component to the plasma disappearance curve is identified with a 30 minute half-life. At two hours essentially all of the interferon activity has been lost from the plasma. The area under the curve was 7047 u/ml x min. In contrast, when the IFG 252.2 antibody is utilized to extend the half-life, a single phase disappearance of activity from plasma is observed. The half-life of this activity loss is 84 minutes. Twelve times longer than that observed for alpha-interferon itself, with a volume of distribution of 19.2 ml, essentially equivalent to that observed for alpha-interferon without added antibody. The area under the curve was 50,000 u/ml x min, seven (7) times that for the free interferon.

The foregoing experiments demonstrate that, by proper selection of an antibody, the serum half-life of a therapeutically active agent can be usefully extended without significant impairment of therapeutic activity.

Those skilled in the art will recognize that the invention, therefore, has application in veterinary medicine and for human health care. In that connection, it is within the scope of the invention to combine the therapeutic agent and/or the antibody or the antibody complex with the agent with other components such as a suitable vehicle. The foregoing description of the invention is exemplary only and modifications thereof may be made without departure from the scope of the invention which is to be limited only by the appended claims.



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Claims:

1. A composition comprising a complex of a therapeutically active agent and an antibody selected to bind said agent at a site which does not substantially impair its therapeutic activity and which extends the serum  
5 half-life of the therapeutically active agent.
2. A composition according to Claim 1 wherein the antibody is a monoclonal antibody.
3. A composition according to Claim 1 wherein the antibody comprises a population of polyclonal antibodies.
- 10 4. A composition according to Claims 2 and 3 wherein the antibody comprises an antibody fragment selected from the group consisting of Fab, Fab' and Fab'2.
5. A composition according to Claim 1 wherein the antibody is a hybrid monoclonal antibody having a dual  
15 specificity one of which is against the therapeutically active agent and the other against a disease associated antigen.
6. A composition according to Claims 1, 2, 3 or 5 wherein the therapeutically active agent is selected from  
20 drugs, toxins and biological proteins.
7. A composition according to Claim 5 wherein the hybrid antibody is an antibody fragment selected from Fab, Fab' and Fab'2.
8. A composition according to Claims 1, 2, 3, 5 or  
25 7 wherein the therapeutically active agent is an interferon.



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9. A composition according to Claim 8 wherein the interferon is selected from alpha, beta and gamma interferons.
10. A composition according to Claims 5 or 7 wherein one specificity of the hybrid antibody is directed against a tumor associated antigen and the other against an agent having anti-tumor activity.
11. A composition according to Claim 10 wherein the tumor associated antigen is selected from CEA, PAP, PSA or ferritin.
12. A composition according to Claim 10 wherein the second specificity is directed against an interferon.
13. A composition according to Claim 1, 2, 3 or 5 further comprising a pharmaceutical vehicle.
14. A process for treatment of disease comprising administering to a patient a therapeutically active agent and an antibody against said agent which binds the agent at a site which does not substantially impair its therapeutic activity and which extends the serum half-life of the agent.
15. A process according to Claim 14 wherein the antibody and agent are combined in vitro.
16. A process according to Claim 14 wherein the antibody and agent are separately administered.
17. A process according to Claim 16 wherein the antibody is allowed to distribute itself throughout the patient prior to administration of the agent.



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18. A process according to Claims 14, 15, 16 or 17 wherein the antibody is a monoclonal antibody.
19. A process according to Claim 18 wherein the monoclonal antibody is a hybrid antibody having a dual  
5 specificity one of which is directed against the therapeutically active agent and the other against a disease associated antigen.
20. A process according to Claim 18 wherein the antibody is a fragment selected from Fab, Fab' and Fab'2.
- 10 21. A process according to Claim 18 wherein the agent is an interferon.
22. A process according to Claim 21 wherein the interferon is selected from alpha, beta and gamma interferons.
23. A process according to Claim 19 wherein the antigen  
15 is a tumor associated antigen and the agent has anti-tumor activity.
24. A process according to Claim 23 wherein the agent is an interferon.
25. A process according to Claim 24 wherein the inter-  
20 feron is selected from alpha, beta and gamma interferons.



# INTERNATIONAL SEARCH REPORT

PCT/US84/01389

International Application No

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>3</sup> According to International Patent Classification (IPC) or to both National Classification and IPC Int. Cl. <sup>8</sup> A61K 39/00, 45/02      US Cl. 424/85																													
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched <sup>4</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border: 1px solid black; text-align: left;">Classification System</th> <th style="border: 1px solid black; text-align: left;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">U. S.</td> <td style="border: 1px solid black; vertical-align: top;">424/85, 86, 87; 260/112R; 435/172.2</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup></div> <p style="text-align: center; padding: 5px;">Chemical Abstracts On Line Computer Search 1967-1984</p>			Classification System	Classification Symbols	U. S.	424/85, 86, 87; 260/112R; 435/172.2																							
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; border: 1px solid black;">Category <sup>6</sup></th> <th style="width: 70%; border: 1px solid black;">Citation of Document, <sup>15</sup> with indication, where appropriate, of the relevant passages <sup>17</sup></th> <th style="width: 20%; border: 1px solid black;">Relevant to Claim No. <sup>18</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4,359,457, published 16 November 1982 Neville et al.</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4,379,145, published 05 April 1983 Masuho et al.</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4,357,273, published 02 November 1982 Masuho et al.</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4,340,535, published 20 July 1982 Voisin et al.</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4,263,279, published 21 Apr. 1981 Sela et al.</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X, P</td> <td style="vertical-align: top;">US, A, 4,414,148, published 08 November 1983 Jansen et al.</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y, P</td> <td style="vertical-align: top;">US, A, 4,423,147, published 27 December 1983 Secher et al.</td> <td style="text-align: center; vertical-align: top;">8,9,12,21, 22, 24, 25</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X, E</td> <td style="vertical-align: top;">US, A, 4,474,893, published 02 October 1984 Reading</td> <td style="text-align: center; vertical-align: top;">1-25</td> </tr> </tbody> </table>			Category <sup>6</sup>	Citation of Document, <sup>15</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>	X	US, A, 4,359,457, published 16 November 1982 Neville et al.	1-25	X	US, A, 4,379,145, published 05 April 1983 Masuho et al.	1-25	X	US, A, 4,357,273, published 02 November 1982 Masuho et al.	1-25	X	US, A, 4,340,535, published 20 July 1982 Voisin et al.	1-25	X	US, A, 4,263,279, published 21 Apr. 1981 Sela et al.	1-25	X, P	US, A, 4,414,148, published 08 November 1983 Jansen et al.	1-25	Y, P	US, A, 4,423,147, published 27 December 1983 Secher et al.	8,9,12,21, 22, 24, 25	X, E	US, A, 4,474,893, published 02 October 1984 Reading	1-25
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>15</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																													
<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;">           Date of the Actual Completion of the International Search <sup>1</sup>  <div style="text-align: center; font-size: 1.2em;">01 November 1984</div> </td> <td style="width: 50%; border: 1px solid black; padding: 5px;">           Date of Mailing of this International Search Report <sup>1</sup>  <div style="text-align: center; font-size: 1.2em;">19 NOV 1984</div> </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">           International Searching Authority <sup>1</sup>  <div style="text-align: center; font-size: 1.2em;">ISA/US</div> </td> <td style="border: 1px solid black; padding: 5px;">           Signature of Authorized Officer <sup>2</sup>  <div style="text-align: center;">              Blondel Hazel           </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <sup>1</sup> <div style="text-align: center; font-size: 1.2em;">01 November 1984</div>	Date of Mailing of this International Search Report <sup>1</sup> <div style="text-align: center; font-size: 1.2em;">19 NOV 1984</div>	International Searching Authority <sup>1</sup> <div style="text-align: center; font-size: 1.2em;">ISA/US</div>	Signature of Authorized Officer <sup>2</sup> <div style="text-align: center;">              Blondel Hazel           </div>																							
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## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X N, Cancer Research, Vol. 35, issued May 1975 (U.S.A.), Hurwitz, E., et al., "The covalent binding of daunomycin and adriamycin to antibodies with retention of both drug and antibody activities", See pages 1175-1181

1-25

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>10</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers \_\_\_\_\_, because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:

2. ☐ Claim numbers \_\_\_\_\_, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out <sup>13</sup>, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>11</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.